Relative Hyperglycemia, a Marker of Critical Illness: Introducing the Stress Hyperglycemia Ratio

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Context: Hyperglycemia in hospitalized patients is associated with increased morbidity and mortality.

Objective: We examined whether critical illness is more strongly associated with relative or absolute hyperglycemia.

Design: The study was an observational cohort study.

Patients and Setting: A total of 2290 patients acutely admitted to a tertiary hospital.

Main Outcome Measure: The relative hyperglycemia (stress hyperglycemia ratio [SHR]) was defined as admission glucose divided by estimated average glucose derived from glycosylated hemoglobin. The relationships between glucose and SHR with critical illness (in-hospital death or critical care) were examined.

Results: In univariable analyses, SHR (odds ratio, 1.23 per 0.1 increment [95% confidence interval, 1.18–1.28]; $P < .001$) and glucose (odds ratio, 1.18 per mmol/L [1.13–1.23]; $P < .001$) were associated with critical illness. In multivariable analysis, the association was maintained for SHR (odds ratio, 1.20 per 0.1 increment [1.13–1.28]; $P < .001$), but not glucose (odds ratio, 1.03 per mmol/L [0.97–1.11]; $P = .31$). Background hyperglycemia affected the relationship between glucose ($P = .002$) and critical illness, but not SHR ($P = .35$) and critical illness. In patients with admission glucose ≤10 mmol/L, the odds ratio for critical illness was higher in the fourth (2.4 [1.4–4.2]; $P = .001$) and fifth (3.9 [2.3–6.8]; $P < .001$) SHR quintiles than in the lowest SHR quintile.

Conclusions: SHR controls for background glycemia and is a better biomarker of critical illness than absolute hyperglycemia. SHR identifies patients with relative hyperglycemia at risk of critical illness. Future studies should explore whether basing glucose-lowering therapy on relative, rather than absolute, hyperglycemia improves outcomes in hospitalized patients. **(*J Clin Endocrinol Metab* 100: 4490–4497, 2015)**

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Abbreviations: CI, confidence interval; HbA_{1c}, glycosylated hemoglobin; ICU, intensive care unit; OR, odds ratio; SHR, stress hyperglycemia ratio.

Hyperglycemia in hospitalized patients is associated with increased morbidity and mortality in patients admitted with a myocardial infarction, congestive cardiac failure, chronic obstructive airway disease, cerebrovascular accident, and critical illness and after surgery for a variety of indications (1–8). This increased risk is often attributed to diabetes. However, mortality rates are higher in patients with new hyperglycemia than in patients with hyperglycemia and known diabetes (1, 7). This finding suggests that differences in baseline glycemia exert an effect on the relationship between glucose and mortality in hospitalized patients.

Hyperglycemia in a hospitalized patient may reflect chronic poor diabetes control and be similar to preadmission glucose levels for that patient, represent a transient physiologic response to an intercurrent illness (stress hyperglycemia), or be a combination of the two. Stress hyperglycemia is the relative increase in glucose due to the inflammatory and neurohormonal derangements that occur during a major illness. The association between hyperglycemia and adverse patient outcomes will, at least partly, reflect that a more severe illness stimulates a greater inflammatory and neurohormonal response. However, stress hyperglycemia may directly contribute to adverse outcomes through mechanisms such as induction of endothelial dysfunction and oxidative stress (9). It is not clear how stress hyperglycemia can be identified in nondiabetic patients at blood glucose concentrations below the recommended 10 mmol/L threshold for glucose-lowering therapy (10, 11). A diagnosis of stress hyperglycemia (relative hyperglycemia) may add prognostic information, and treatment could potentially reduce mortality and morbidity.

Glycosylated hemoglobin (HbA_{1c}) is a well-validated measure of glycemia over the previous 8 to 12 weeks and can be translated into an estimated average glucose concentration during this time period (12, 13). In this study, we used HbA_{1c} to calculate background glycemia and its relationship with admission glucose to estimate relative hyperglycemia and to identify and quantify stress hyperglycemia. We then assessed whether critical illness was more strongly related to relative hyperglycemia than absolute hyperglycemia. In secondary analyses, we compared these relationships in patients with and without background hyperglycemia and determined whether SHR identifies patients at increased risk of critical illness with glucose concentrations below the recommended 10 mmol/L threshold for glucose-lowering therapy (10, 11).

Materials and Methods

Subjects

This is a secondary analysis of data obtained from a prospective cohort study investigating the utility of HbA_{1c} to diagnose diabetes in hospitalized patients (14). Between April 1 and June 30, 2009, 4691 adult nonobstetric patients were admitted to Flinders Medical Centre, Adelaide, Australia. Of the 3873 consecutive patients who had a blood test within 24 hours of admission, 2672 patients had a laboratory glucose concentration $\geq$5.5 mmol/L. This triggered measurement of HbA_{1c} in the admission blood sample. If patients were admitted more than once during the study period, only the first admission with a glucose $\geq$5.5 mmol/L was included in the analysis.

This analysis is of a cohort of 2290 patients acutely admitted to medical or surgical services. We excluded 382 patients admitted for prespecified criteria including treatment of hyperglycemia or diabetic ketoacidosis, routine dialysis, chemotherapy, day surgery, psychiatric illness, acute poisoning, and overdose. Patients admitted to the obstetrics and gynecology unit and to the intensive care unit (ICU) for reasons other than an acute illness (ie, protocol-driven postoperative monitoring) were also excluded (Figure 1).

Demographic data, laboratory data, and in-hospital mortality were obtained from hospital databases. Participants received usual care from their treating physicians. Treating physicians had access to all blood glucose results, but not HbA_{1c}, which was not a recognized diagnostic test for diabetes in Australia at that time. The study was approved by the Southern Adelaide Clinical Research Ethics Committee; patient consent was not required.

Assessment of hyperglycemia

HbA_{1c} was used to estimate the average blood glucose concentration before admission using the equation, estimated average glucose = $(1.59 \times HbA_{1c}) - 2.59$, derived by Nathan et al (13). Relative hyperglycemia was defined by the SHR, calculated as admission blood glucose divided by estimated average glucose. HbA_{1c} was also used to designate the absence or presence of background hyperglycemia before admission (HbA_{1c} of $<$6.5% [48 mmol/mol] and $\geq$6.5%, respectively).

Samples were batched for measurement of HbA_{1c} by HPLC (PDQ; Primus Diagnostics) using boronate affinity chromatog-

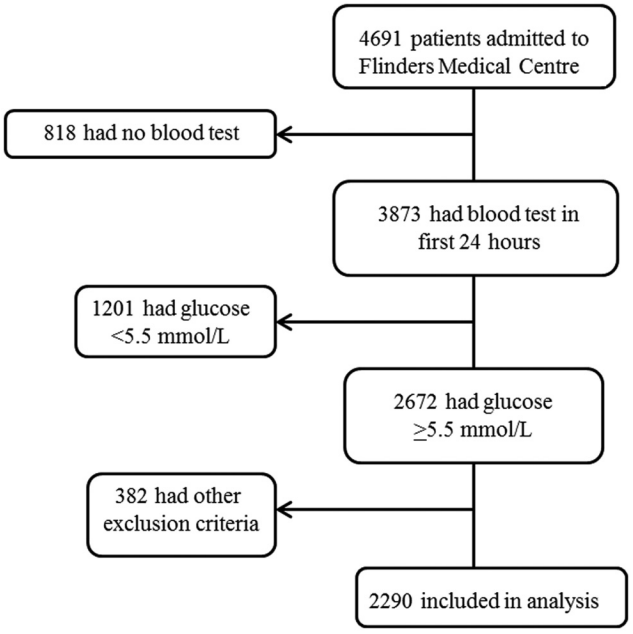

Figure 1. Flow diagram outlining selection of the study cohort.

Table 1. Whole Cohort Characteristics and Characteristics of Patients With HbA_{1c} of <6.5% (48 mmol/mol) and HbA_{1c} of ≥6.5%

	All Patients	HbA_{1c}		*P* Value
		<6.5%	≥6.5%	
n	2290	1907	383	
HbA_{1c}, %	5.7 (5.4–6.1)	5.6 (5.3–5.9)	7.1 (6.7–8.0)	
Age-y	65.1 (19.5)	64.3 (20.1)	69.1 (15.2)	<.001
Male, n (%)	1194 (52.1)	981 (51.4)	213 (55.6)	.14
Length of stay, d	3.3 (1.2–7.8)	3.2 (1.2–7.8)	3.6 (1.5–7.6)	.20
GFR, mL/min	85.9 (40.9)	87.1 (41.5)	80.1 (37.4)	.002
Hb, g/L	129.6 (20.7)	129.8 (20.9)	128.5 (19.5)	.24
Glucose, mmol/L	6.8 (6.0–8.2)	6.5 (5.9–7.6)	9.1 (7.2–12)	<.001
SHR	1.11 (0.27)	1.12 (0.25)	1.05 (0.33)	<.001

Abbreviations: GFR, glomerular filtration rate; Hb, hemoglobin. Data are expressed as means (SD) or medians (interquartile range) unless otherwise stated. *P* values compare the HbA_{1c} of <6.5% (48 mmol/mol) and HbA_{1c} of ≥6.5% subgroups.

raphy (between-run coefficient of variation of 2.2% at HbA_{1c} of 6.1% [43 mmol/mol] and 1.9% at HbA_{1c} of 11.1% [98 mmol/mol]). Venous plasma glucose was measured on a Roche P modular analyzer (Hitachi High-Technologies Corporation) using the hexokinase/glucose-6-phosphate dehydrogenase assay (between-run coefficient of variation of 1.7% at a glucose level of 4.9 mmol/L and 1.4% at a glucose level of 15.7 mmol/L).

Statistical analysis

The primary endpoint was critical illness, defined for study purposes as either in-hospital death or admission to the ICU. The primary variables of interest were admission glucose concentration and SHR calculated using this glucose measurement. The characteristics of patients with and without background hyperglycemia were compared using unpaired *t* tests, Mann-Whitney U tests, or χ^2 tests as appropriate. Univariable and multivariable logistic regression were used to examine the associations between clinical outcomes and variables of interest, which included blood glucose, SHR, age, sex, ethnicity, hemoglobin, and glomerular filtration rate. All models were validated using the Hosmer-Lemeshow goodness-of-fit statistic, and no evidence of model violation was found ($P = .50$). Locally weighted scatterplot smoothing curves were used to graphically depict the relationship of glucose and SHR with the primary endpoint, as well as death and ICU admission individually in the whole cohort and in subgroups with and without background hyperglycemia. We calculated interaction terms to determine whether the relationships between glucose with critical illness and SHR with critical illness were moderated by background glycemia. Odds ratios for quintiles of SHR were calculated in patients with admission glucose levels of <10 mmol/L to define thresholds of SHR associated with increased risk of critical illness in this group.

All statistical analyses were performed with Stata version 12.1 with a two-tailed *P* value of <.05 considered statistically significant.

Results

Patient characteristics

The patient characteristics are presented in Table 1. Of the patients, 16.7% (383 of 2290) had HbA_{1c} ≥6.5% (48 mmol/mol). These patients were older and had poorer renal function, higher glucose concentration, and lower SHR than those with HbA_{1c} <6.5%. Of the 383 patients with background hyperglycemia, 156 (40.7%) had known

Table 2. Univariable and Multivariable ORs for the Relationships Between Selected Variables and Critical Illness (Death or ICU Admission)

	Univariable analyses			Multivariable analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Glucose, mmol/L	1.18	1.13–1.23	<.001	1.03	0.97–1.11	.31
SHR per 0.1 increment	1.23	1.18–1.28	<.001	1.20	1.13–1.28	<.001
Age per decade	1.04	0.97–1.11	.25	0.96	0.89–1.03	.24
Male sex	1.61	1.25–2.06	<.001	2.05	1.57–2.67	<.001
Non-Caucasian	1.06	0.65–1.70	.83	1.17	0.71–1.91	.55
Hb per 10 g/L	0.82	0.77–0.86	<.001	0.79	0.75–0.85	<.001
GFR per 10 mL/min)	1.00	0.99–1.00	.058	1.00	0.99–1.00	.38

Abbreviations: GFR, glomerular filtration rate; Hb, hemoglobin.

diabetes and 227 (59.3%) were not previously known to have diabetes. Of the patients without background hyperglycemia, 79 had a previous diagnosis of diabetes. Of the patients admitted to the ICU, 63.5% were admitted directly from the emergency department, with the remainder transferred to the ICU after initial admission to the general wards.

Whole cohort

Critical illness occurred in 229 (13.1%) patients; 86 (3.1%) patients died and 246 (10.7%) were admitted to the ICU. In univariable analyses, both glucose (odds ratio [OR], 1.18; 95% confidence interval [CI], 1.13–1.23) and SHR (OR, 1.23; 95% CI, 1.18–1.28) were positively associated with critical illness (Table 2 and Figure 2). The relationships between SHR and in-hospital death or ICU admission individually were similar to the combined endpoint (Figure 2). In a multivariable logistic regression containing glucose, SHR, and other defined variables, SHR was independently associated with critical illness (Table 2), with each 0.1 increase associated with a 20% increase in critical illness (OR, 1.20; 95% CI, 1.13–1.28). Male sex and lower hemoglobin were also independently associated with an increased incidence of critical illness (Table 2). In contrast, admission glucose was not independently associated with critical illness (OR, 1.03; 95% CI, 0.97–1.11).

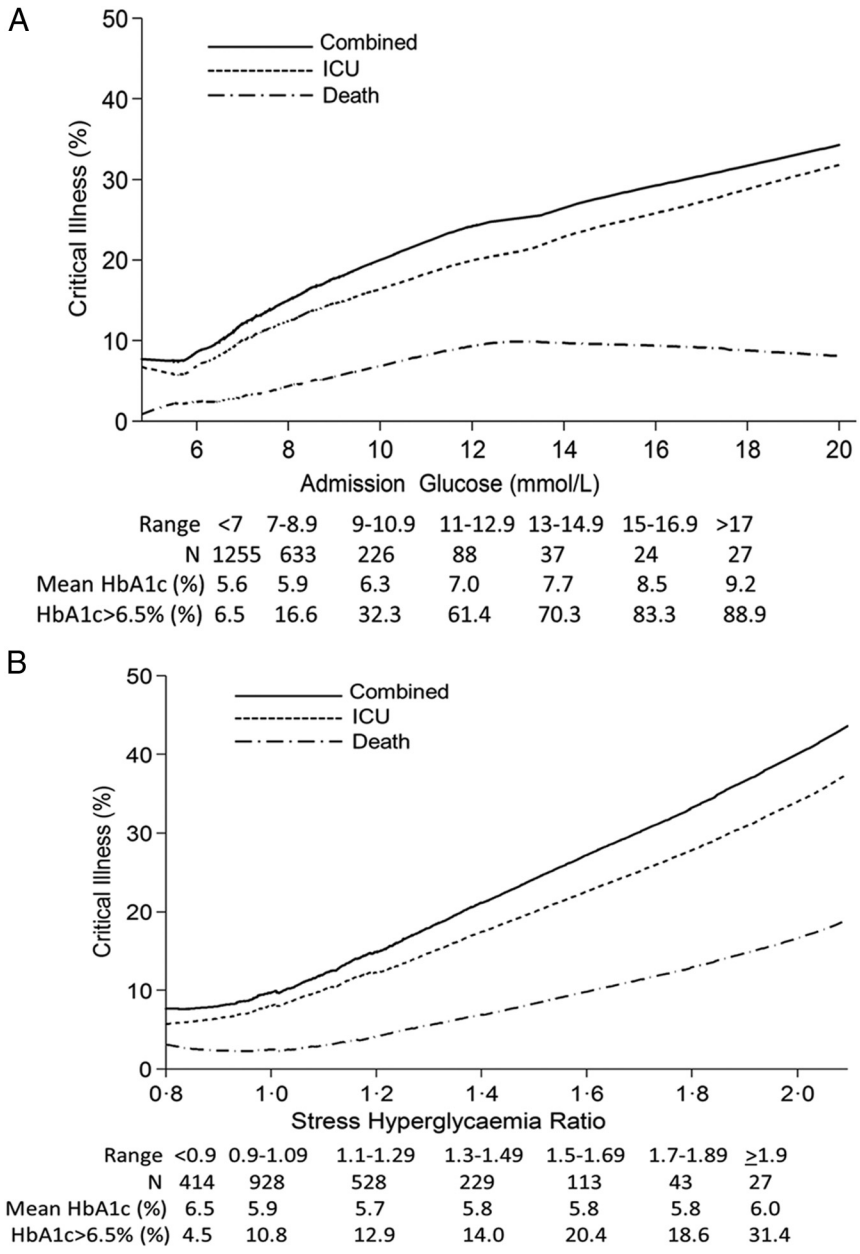

Figure 2. Rate of critical illness according to admission glucose concentration (A) and SHR (B).

Patients with and without prior background hyperglycemia

Critical illness occurred in 12.8% (49 of 383) of patients with HbA_{1c} ≥6.5% (48 mmol/mol) and 13.1% (250 of 1907) of patients with HbA_{1c} <6.5% (P = .87). The mortality rates were 3.7% and 3.8% (P = .91) and the ICU admission rates were 10.4% and 10.8% (P = .84), respectively. For any given glucose concentration, patients with HbA_{1c} <6.5% (48 mmol/mol) had a greater risk of critical illness than patients with HbA_{1c} ≥6.5% (Figure 3A), with a significant interaction between glucose concentration and background hyperglycemia (P = .002). In contrast, for any given SHR, the percentage of patients experiencing critical illness was similar in patients with HbA_{1c} ≥6.5% (48 mmol/mol) and <6.5% (Figure 3B), with no significant interaction between SHR and background hyperglycemia (P = .35).

Patients with admission glucose level of <10 mmol/L

When categorized into quintiles for increasing SHR, the fourth and fifth highest quintiles of patients had ORs for critical illness that were increased by 2.4 (95% CI, 1.40–4.15) and 3.9 (95% CI, 2.28–6.77), respectively, compared with the first quintile (Figure 4). The OR for quintile 5 was significantly higher than that for quintile 4 (P = .012).

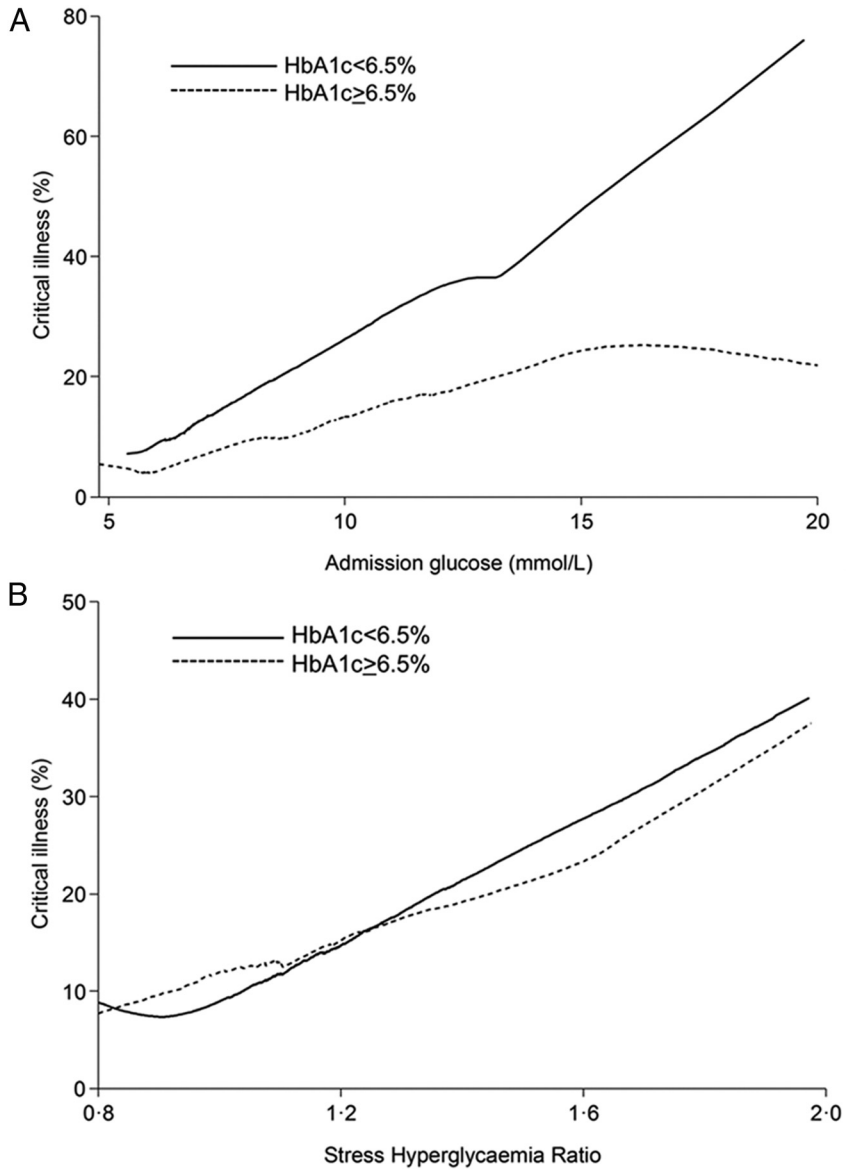

Figure 3. HbA_{1c} of <6.5% or ≥6.5% and the rate of critical illness according to admission glucose concentration (A) and SHR (B).

Discussion

The results of this study suggest that, because SHR controls for background glycemia, it is a better biomarker of critical illness than absolute hyperglycemia in patients across the glycemic spectrum. When both admission glucose and SHR were included in a multivariable analysis, SHR was independently associated with critical illness, whereas glucose was not. We also found that SHR performs similarly in patients with or without background hyperglycemia and that it identifies patients with relative hyperglycemia at an increased risk of critical illness at glucose concentrations of <10 mmol/L. As glucose and HbA_{1c} tests are widely available and SHR is simple to calculate, these could be used to provide prognostic information in hospitalized patients.

A number of studies have previously compared the relationship between glucose concentration on admission with the hospital and patient outcomes (1–8). Consistent with previous studies, in this cohort of hospitalized patients, the admission glucose concentration was associated with a poor outcome in a univariable analysis.

However, the relationship between glucose concentrations and patient outcomes is complex. Previous studies have reported that underlying diseases (15), known diabetes (16, 17), or background hyperglycemia (18) can affect the association between glucose and patient outcomes.

Differences in relative hyperglycemia may underlie variability in the association between glucose concentrations and adverse outcomes in hospitalized patients. Absolute admission glucose is substantially affected by a patient's baseline glycemia. It has previously been hypothesized that correcting the glucose level for HbA_{1c} to calculate relative hyperglycemia may provide new insights into the relationship between hyperglycemia and patient outcomes (20). One study reported that complications in patients with pyogenic liver abscesses occur more frequently in patients with an admission glucose level of >4 mmol/L higher than their estimated average glucose level derived from HbA_{1c} (21). However, the relationship between relative hyperglycemia and patient outcomes has not been assessed in other patient groups. We have undertaken the first systematic comparison of the relationships between absolute and relative hyperglycemia and critical illness in a large group of hospitalized patients.

Our results indicate that relative hyperglycemia is a better biomarker of critical illness than absolute hyperglycemia. When compared in a multiple regression analysis, relative hyperglycemia as defined by SHR was independently associated with critical illness, whereas absolute hyperglycemia was not. This is analogous to the prognostic superiority of body mass index over body weight as a predictor of health outcomes (22, 23). Al-

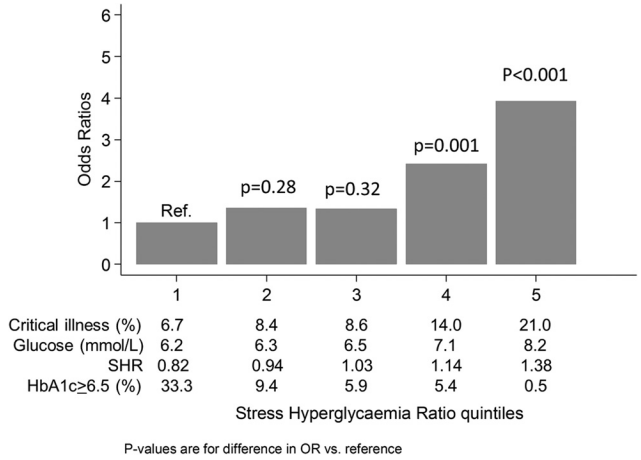

Figure 4. ORs for critical illness for each SHR quintile in patients with glucose of <10 mmol/L. Glucose and SHR values are the means for each quintile. HbA_{1c} of ≥6.5% (%) is the percentage of patients with HbA_{1c} of ≥6.5% in each quintile.

though weight is associated with cardiovascular disease and diabetes, correction of weight for height identifies patients at risk who are otherwise not identified by weight alone. Similarly, correction of absolute glycemia for background glycemia may refine the risk assessment associated with hyperglycemia in hospitalized patients.

Unlike absolute hyperglycemia, the relationship between relative hyperglycemia and critical illness was not affected by background glycemia. At any given glucose concentration, the rates of critical illness were higher in patients with HbA_{1c} of <6.5% (48 mmol/mol) than in those with HbA_{1c} of ≥6.5% (Figure 2A). These findings are consistent with previous studies reporting that hospitalized patients with new hyperglycemia have poorer outcomes than patients with known diabetes and a similar degree of hyperglycemia (1, 8, 24). It has been hypothesized that background hyperglycemia might protect against the adverse consequences of stress hyperglycemia, through putative mechanisms such as down-regulation of glucose transporters (9). However, the analysis of SHR suggests that this is not the case. The same degree of relative hyperglycemia is associated with the same risk of critical illness in patients with and without background hyperglycemia (Figure 2B), and there was not a significant interaction between SHR and background hyperglycemia. By correcting for background glycemia, SHR allows uniform clinical risk stratification of stress hyperglycemia across the glycemic range encountered in clinical practice.

Previous studies have reported that stress hyperglycemia with an absolute glucose concentration of <10 mmol/L is associated with adverse patient outcomes (25, 26). However, guidelines recommend initiating glucose-lowering therapy in hospitalized patients when the glucose level exceeds 10 mmol/L (10, 11). Our study demonstrates that patients with relative hyperglycemia but not absolute hyperglycemia are at increased risk of critical illness. In patients with a glucose concentration <10 mmol/L, the highest SHR quintile (mean SHR of 1.38) had a rate of critical illness of 21%, nearly double the rate of the entire cohort and 4 times the rate in the lowest SHR quintile. More than 99% of patients in this quintile had an HbA_{1c} <6.5% (48 mmol/mol), and the mean glucose concentration was 8.2 mmol/L. Furthermore, patients in quintile 4, with only a modest increase in SHR (mean SHR of 1.14), had an OR for admission to the ICU or death that was more than double that for the lowest quintile, despite a mean glucose level of only 7.1 mmol/L. SHR may identify patients with relative hyperglycemia at glucose concentrations below the conventional threshhold for glucose-lowering therapy of 10 mmol/L who are at increased risk of critical illness.

Future studies could expand on the relationship between relative hyperglycemia and patient outcomes. We used admission glucose to calculate SHR because it was available for all patients and allows risk stratification of patients soon after their admission to the hospital. However, persistent hyperglycemia during a hospital admission is a better predictor of mortality than admission glucose (24). Thus, quantification of changes in relative hyperglycemia over the course of a hospital admission may improve its prognostic significance. There may also be other variables of importance, such as intermittent hyperglycemia, which is associated with greater endothelial dysfunction and oxidative stress (27, 28).

Another area that requires clarification is the relationship between SHR and critical illness at the lower end of the SHR range. The relationship between glucose and mortality in patients with acute myocardial infarctions is J-shaped, with increased mortality rates when the glucose concentration is <3.9 mmol/L (29). Because the primary aim of this study was to determine the rate of diabetes in hospitalized patients, HbA_{1c} was not measured in patients with glucose concentrations of <5.5 mmol/L. Further studies are needed to define the relationship between relative hyperglycemia and patient outcomes at lower glucose concentrations.

Although our data suggest that SHR could provide prognostic information in hospitalized patients, further studies are needed to test whether it has therapeutic utility. Intensive glycemic control after cardiothoracic surgery was reported to improve outcomes in patients without known diabetes but not in patients with a previous diagnosis of diabetes (30). Others have suggested that therapeutic glycemic targets in critically ill patients should vary depending on the presence or absence of diabetes or background glycemia (31, 32). The observed association between SHR and critical illness may provide a rationale for

future interventional studies or provide stimulation for reassessment of existing data sets. If the results of these studies were positive, glucose and HbA_{1c} tests are widely available and SHR is simple to calculate and thus could be readily incorporated into clinical practice.

The strengths of this study include the recruitment of a large cohort of consecutive hospitalized patients with an acute physiologic illness. Careful patient selection ensured that relative increases in glucose were likely to be due to stress hyperglycemia. However, we acknowledge that the study has limitations. First, this is a secondary analysis of an observational study and is therefore hypothesis generating. However, we minimized any bias in the analysis because we clearly defined the research question before undertaking the statistical analysis. Second, although we accounted for the available variables in regression modeling, there are a number of patient variables known to be associated with adverse outcomes that were not available. Hence, it is possible that SHR is a surrogate for other variables not studied, and this needs to be investigated in more detailed data sets. In particular, markers of disease severity were not recorded in this heterogeneous group of patients. Thus, further studies are required to assess whether the relationship between SHR and critical illness is independent of other readily available biomarkers, eg, serum lactate (33, 34). Third, we do not have data demonstrating that glucose fell after hospitalization to confirm that glucose elevations were secondary to an intercurrent illness (ie, stress hyperglycemia). Fourth, the number of events was insufficient to power further subgroup analyses. Fifth, we are unable to account for the effect of treating hyperglycemia while patients were in the hospital on rates of critical illness. Finally, measurements of HbA_{1c} are spuriously low in some patients, such as those with anemia, recent blood transfusions, and increased red blood cell turnover, which may reduce the sensitivity of SHR (35).

In conclusion, relative hyperglycemia, as measured by the SHR, was more strongly associated with critical illness than absolute hyperglycemia. By controlling for individual patient background glycemia, SHR is an independent predictor of critical illness in patients across the glycemic spectrum. SHR can identify patients with relative hyperglycemia at an increased risk of critical illness below the usual hospital threshold for glucose-lowering therapy. Pending independent verification of SHR, future studies should explore whether basing glycemic therapy on relative, rather than absolute, hyperglycemia improves patient outcomes.

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References

1. **Umpierrez GE, Isaacs SD, Bazargen N, You X, Thaler LM, Kitabchi AE.** Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab*. 2002;87:978–982.
2. **Krinsley J.** Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc*. 2003;78:1471–1478.
3. **Baker EH, Janaway CH, Philips BJ, et al.** Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. *Thorax*. 2006;61:284–289.
4. **Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC.** Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke*. 2001;32:2426–2432.
5. **Iglesias P, Polini A, Muñoz A, et al.** Fasting hyperglycaemia and in-hospital mortality in elderly population. *Int J Clin Pract*. 2011; 65:308–313.
6. **Barsheshet A, Garty M, Grossman E, et al.** Admission blood glucose level and mortality among hospitalized nondiabetic patients with heart failure. *Arch Intern Med*. 2006;166:1613–1619.
7. **Capes SE, Hunt D, Malmberg K, Gerstein HC.** Stress Hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet*. 2000;355:773–778.
8. **Vreisendorp TM, Morélis QJ, Devries JH, Legemate DA, Hoekstra JB.** Early post-operative glucose levels are an independent risk factor for infection after peripheral vascular surgery. A retrospective study. *Eur J Vasc Endovasc Surg*. 2004;28:520–525.
9. **Dungan KM, Braithwaite SS, Preiser JC.** Stress hyperglycaemia. *Lancet*. 2009;373:1798–1807.
10. **American Diabetes Association.** Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14–S80.
11. **Umpierrez GE, Hellman R, Korytkowski MT, et al.** Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97:16–38.
12. **Nathan DM, Turgeon H, Regan S.** Relationship between glycated haemoglobin levels and mean glucose levels over time. *Diabetologia*. 2007;50:2239–2244.
13. **Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ.** Translating the A1C assay into estimated average glucose values. *Diabetes Care*. 2008;31:1473–1478.
14. **Valentine NA, Alhawassi TM, Roberts GW, Vora PP, Stranks SN, Doogue MP.** Detecting undiagnosed diabetes using glycated hemo-

globin: an automated screening test in hospitalised patients. *Med J Aust*. 2011;194:160–164.
15. **Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML.** Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med*. 2009;37:3001–3009.
16. **Kotagal M, Symons RG, Hirsch IB, et al.** Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. *Ann Surg*. 2015;261:97–103.
17. **Frisch A, Chandra P, Smiley D, et al.** Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. *Diabetes Care*. 2010;33:1783–1788.
18. **Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Taori G, Hegarty C, Bailey M.** The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. *Crit Care Med*. 2011;39:105–111.
19. **Ascione R, Rogers CA, Rajakaruna C, Angelini GD.** Inadequate blood glucose control is associated with in-hospital mortality and morbidity in diabetic and nondiabetic patients undergoing cardiac surgery. *Circulation*. 2008;118:113–123.
20. **Braithwaite S.** Through the eyes of the A1C: a call to re-examine stress hyperglycemia. *Crit Care Med*. 2010;38:717–719.
21. **Liao WI, Sheu WH, Chang WC, Hsu CW, Chen YL, Tsai SH.** An elevated gap between admission and A1C-derived average glucose levels is associated with adverse outcomes in diabetic patients with pyogenic liver abscess. *PLoS One*. 2013;8:e64476.
22. **Wilson PW, D'Agostini R, Sullivan L, Parise H, Kannel WB.** Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med*. 2002;162:1867–1872.
23. **Colditz GA, Willett WC, Rotnitzky A, Manson JE.** Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med*. 1995;122:481–486.
24. **Kosiborod M, Inzucchi SE, Krumholz HM, et al.** Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. *Circulation*. 2008;117:1018–1027.
25. **Schuetz P, Kennedy M, Lucas JM, et al.** Initial management of septic patients with hyperglycemia in the noncritical care inpatient setting. *Am J Med*. 2012;125:670–678.
26. **Chen Y, Yang X, Meng K, et al.** Stress-induced hyperglycemia after hip fracture and the increased risk of acute myocardial infarction in nondiabetic patients. *Diabetes Care*. 2013;36:3328–3332.
27. **Monnier L, Mas E, Ginet C, et al.** Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA*. 2006;295:1681–1687.
28. **Ceriello A, Esposito K, Piconi L, et al.** Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes*. 2008;57:1349–1354.
29. **Lee SA, Cho SJ, Jeong MH, et al.** Hypoglycemia at admission in patients with acute myocardial infarction predicts a higher 30-day mortality in patients with poorly controlled type 2 diabetes than in well-controlled patients. *Diabetes Care*. 2014;37:2366–2373.
30. **Umpierrez G, Cardona S, Pasquel F, et al.** Randomized controlled trial of intensive versus conservative glucose control in patients undergoing coronary artery bypass graft surgery: GLUCO-CABG Trial. *Diabetes Care*. 2015;38:1665–1672.
31. **Krinsley JS, Egi M, Kiss A, et al.** Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. *Crit Care*. 2013;17:R37.
32. **Marik PE, Egi M.** Treatment thresholds for hyperglycemia in critically ill patients with and without diabetes. *Intensive Care Med*. 2014;40:1049–1051.
33. **Green JP, Berger T, Garg N, et al.** Hyperlactatemia affects the association of hyperglycemia with mortality in nondiabetic adults with sepsis. *Acad Emerg Med*. 2012;19(11):1268–1275.
34. **Kaukonen KM, Bailey M, Egi M, et al.** Stress hyperlactatemia modifies the relationship between stress hyperglycemia and outcome: a retrospective observational study. *Crit Care Med*. 2014;42:1379–1385.
35. **Kilpatrick ES, Bloomgarden ZT, Zimmet PZ.** Is haemoglobin A_{1c} a step forward for diagnosing diabetes? *BMJ*. 2009;339:1288–1290.